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(54) **Title:** TREATMENT OF NEUROPATHIC PAIN

(57) **Abstract:** The present invention relates the use of a spiro-piperidine compounds for the preparation of a medicament useful for the treatment of neuropathic pain.

TREATMENT OF NEUROPATHIC PAIN

Field of invention

The present invention relates to the use of certain spiro-piperidine compounds for the preparation of medicaments useful for the treatment of neuropathic pain.

Background of the Invention

Neuropathic pain refers clinically to a group of cronic pain syndromes. They share the common feature that they are caused by an initial nerve damage which subsequently results in an abnormal sensoric processing in the central and peripheral nervous system. Neuropathic pain conditions are the consequence of a number of diseases, e.g. diabetes, AIDS, multiple sclerosis, amputees and cancer. The available analgetic drug do often produce insufficient pain relief. Tricyclic antidepressants and some antiepileptic drugs, e.g. gabapentin, lamotrigine and carbamazepine are efficient in some patients. However, there is still a large unmet need for efficient drugs for the treatment of these conditions.

It has now, surprisingly, been found that certain spiro-piperidines disclosed in WO 92/22554 show a beneficial effect in the treatment of neuropathic pain.

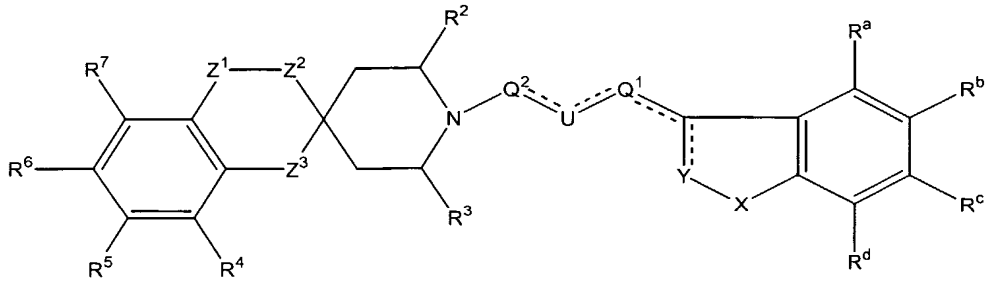
The compounds disclosed in WO 92/22554 are described therein as sigma receptor ligands and are considered useful for the treatment of a range of psychiatric and neurological disorders, including psychosis, movement disorders, such as dystonia and tardive dyskinesia, motor disturbances associated with Huntington's chorea or Tourette's syndrome and in Parkinson's, ischemia, epilepsy, convulsion, amnesia, senile dementia of the Alzheimer type and anxiety.

No references seem to imply that compounds with effect at sigma receptors would be useful for the treatment of neuropathic pain.

Description of the Invention

According to the present invention a medicament for the treatment of neuropathic pain is provided.

More specifically, the present invention relates to the use of a a spiro-piperidine compound having the general formula (I)



(I)

wherein X is CHR^{10}, O, S, SO, SO_2 or NR^{10}, R^{10} being hydrogen, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_3–C_8 cycloalkyl, adamantyl or C_3–C_8 cycloalkyl(C_1–C_6)alkyl, C_3–C_8 cycloalkenyl or C_3–C_8 cycloalkenyl(C_1–C_6)alkyl, C_1–C_6 alkylcarbonyl, phenylcarbonyl, amino(C_1–C_6)alkyl, mono- or di(C_1–C_6)alkylamino(C_1–C_6)alkyl, C_1–C_6 sulfonyl , phenylsulfonyl, or phenyl(C_1–C_6)alkyl or phenyl optionally substituted with one or more substituents independently selected from the following: halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, hydroxy, trifluoromethyl, and cyano, or R^{10} is 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-thiazolyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

one or two of the dotted lines may be a bond;

when the dotted line emanating from Y indicates a bond, Y is N or CH; or

when said dotted line indicates no bond, Y is CH_2, NH, C=O or C=S;

R^a – R^d are independently selected from hydrogen, halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, hydroxy, C_1–C_6 alkylthio, C_1–C_6 alkylsulphonyl, C_1–C_6 alkyl- or di(C_1–C_6)alkylamino, cyano, trifluoromethyl, or trifluoromethylthio;

U is CH_2, O or S; or when, one of the dotted lines emanating from U indicates a bond, U is CH; the bond between Q^1 or Q^2, respectively, and U may also be a triple bond and in such case U is "C";

Q^1 is selected from a bond, alkylene or alkenylene and Q^2 is alkylene having at least two C-atoms, alkenylene or a group Q^3D wherein Q^3 is alkylene having at least two C-atoms, or alkenylene and D is CR^8R^9 where R^8 and R^9 are independently selected from the substituents defined below for R^4 - R^7, Q^1 and Q^2 having together from 2 to 20 carbon atoms and being optionally substituted with one or more hydroxy groups, any such hydroxy group being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive; and

R^2 and R^3 are independently hydrogen, C_1–C_6 alkyl or they may be linked together thereby forming an ethylene or propylene bridge;

R^4 to R^7 are independently selected from hydrogen, halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, hydroxy, C_1–C_6 alkylthio, C_1–C_6 alkyl- or di(C_1–C_6)alkylamino, cyano, trifluoromethyl, or trifluoromethylthio; and

Z^1 is CH_2, O or S;
Z^2 and Z^3 are independently a bond, CH_2, O or S, with the proviso that Z^1 may not be S or O when Z^2 is S or O, and that Z^2 and Z^3 may not both be a bond;
or Z^1 and Z^2 may together represent a group -CH=CH-;
or when Z^3 is a bond, Z^1 and Z^2 may together represent a 3-membered divalent group containing one O- or S-heteroatom; or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment of neuropathic pain.

In particular the present invention relates to the use as above of a compound wherein at least one of Z^1, Z^2 and Z^3 designates O or S.

In one embodiment the present invention relates to the use as above of a compound wherein Z^3 is a bond, and Z^2 is "O" or "S" and Z^1 is CH_2.

In particular, the present invention relates the use of such compounds wherein X is O, S or NR^{10} wherein R^{10} is C_1–C_6 alkyl, C_2–C_6 alkenyl, C_3–C_8 cycloalkyl, adamantyl or C_3–C_8 cycloalkyl(C_1–C_6)alkyl, C_3–C_8 cycloalkenyl or C_3–C_8 cycloalkenyl(C_1–C_6)alkyl, C_1–C_6 alkylcarbonyl, phenylcarbonyl, amino(C_1–C_6)alkyl, mono- or di(C_1–C_6)alkylamino(C_1–C_6)alkyl, C_1–C_6 alkylsulfonyl, phenylsulfonyl, or phenyl(C_1–C_6)alkyl or optionally substituted phenyl.

In particular, the present invention relates to the use of such compounds wherein Y is CH and the dotted line emanating from Y indicates a bond.

In another embodiment, the present invention relates to the use as above of a compound wherein X is O.

In a further embodiment, the present invention relates to the use as above of a compound wherein X is NR^{10} wherein R^{10} is optionally substituted phenyl.

In a specific embodiment, the present invention relates to the use of a compound selected from the following:
1'-[2-(5-Fluorobenzofuran-3-ylmethyloxy)-1-ethyl]spiro[isobenzofuran-1(*3H*),4'-piperidine], and
1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine], or or a pharmaceutically acceptable salt thereof.

The terms C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, etc. designate such branched or unbranched groups having from one to six carbon atoms. Exemplary of such groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, methoxy, ethoxy,1-propoxy, 2-propoxy, methylthio, ethylthio, 1-propylthio, 2-propylthio, methylsulphonyl, ethylsulphonyl, or the like.

The term C_{3-8}-cycloalkyl designates a carbocyclic ring having 3-8 carbon, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Halogen means fluoro, chloro, bromo or iodo.

The term "one or two of the dotted lines may be a bond" is intended to mean that each of the dotted lines may or may not represent a bond, i.e. that the ring and the side chain respectively may or may not have a double bond in the positions of the dotted lines, provided that only two at a time indicate a bond and that adjacent dotted lines do not both indicate a bond.

The compounds which may be used according to the present invention may be prepared as described in WO 92/22554.

The above application specifically describes the preparation of the following compounds which may be useful according to the present invention:

1'-[4-(3-Indolyl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-[4-(3-Indolyl)-1-butyl]-spiro[1*H*-2-benzopyran-4(3*H*),4'-piperidine],
1'-[5-(3-Indolyl)-1-pentyl]-spiro[1*H*-2-benzopyran-4(3*H*),4'-piperidine],
1'-[6-(3-Indolyl)-1-hexyl]-spiro[1*H*-2-benzopyran-4(3*H*),4'-piperidine],
1'-[4-(5,6-Dichloro-3-indolyl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-[4-(5-Fluoro-3-indolyl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-[4-(1-Methyl-3-indolyl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],
6-Fluoro-1'-(4-(3-indolyl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],
1,4-Dihydro-1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]spiro[3*H*-2-benzopyran-3,4'-piperidine],
1'-[4-[1-(3-Thienyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-[4-[1-(2-Thienyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-[4-[1-(3-Furanyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-[4-[1-(4-Pyridyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-(4-(1-Methanesulfonyl-3-indolyl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],
1'-(4-(1-*p*-Toluenesulfonyl-3-indolyl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],

6-Fluoro-1'-(4-(1-(2-thienyl)sulfonyl-3-indolyl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-(4-(1-Acetyl-3-indolyl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[3-[1-(4-Fluorophenyl)-3-indolyloxy]-1-propyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[3-[6-Chloro-1-(4-fluorophenyl)-3-indolyloxy]-1-propyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[3-[5-Chloro-1-(4-fluorophenyl)-3-indolyloxy]-1-propyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]spiro[1*H*-2-benzopyran-4(3*H*),4'-piperidine],

1'-[4-[5-Fluoro-1-(4-fluorophenyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]spiro[benzo[c]thiophene-1(3*H*),4'-piperidine],

8'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butylspiro[isobenzofuran-1(*3H*),3'-8-azabicyclo[3,2,1]octane],

6-Fluoro-1'-[4-[1-(4-fluorophenyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]-6-isopropylspiro[isobenzofuran-1(3*H*),4'-piperidine],

7-Fluoro-1'-[4-[1-(4-fluorophenyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]-5-methylspiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-[1-(4-Methylphenyl)-3-indolyl]-1-butyl]spiro[1*H*-2-benzopyran-4(3*H*),4'-piperidine],

1'-[4-[5-Fluoro-1-(3-thienyl)-3-indolyl]-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-[1-(3-Pyridinyl)-3-indolyl]-1-butyl]spiro[1*H*-2-benzopyran-4(3*H*),4'-piperidine],

1'-[4-(1-(2-Thiazolyl)-3-indolyl)-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

6-Trifluoromethyl-1'-[4-[1-(4-fluorophenyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

4-Fluoro-1'-[4-[1-(4-fluorophenyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

2,3-Dihydro-1'-[4-[1-(4-fluorophenyl)-3-indolyl]-1-butyl]spiro[4*H*-1-benzopyran-4,4'-piperidine],

6-Fluoro-1'-[4-[5-fluoro-1-(4-fluorophenyl)-3-indolyl]-1-butyl]spiro[isobenzofuran-1(*H*),4'-piperidine],

1'-(4-(Benzo[b]thiophen-3-yl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],.

1,4-Dihydro-1'-(4-(benzo[b]thiophen-3-yl)-1-butyl)spiro[3*H*-2-benzopyran-3,4'-piperidine],

1'-(4-(5-Methylbenzo[b]thiophen-3-yl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[3-(2,3-Dihydro-5-fluoro-benzofuran-3-yl)-1-propyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-(2,3-Dihydro-5-fluoro-benzofuran-3-yl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-(2,3-Dihydro-3-indolyl)-1-butyl]spiro[1,3-benzodioxole-2,4'-piperidine],

1'-[4-(2,3-Dihydro-3-indolyl)-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-(2,3-Dihydro-3-indolyl)-1-butyl]spiro[1*H*-2-benzopyran-4(3*H*),4'-piperidine],

1'-[2-[5-Chloro-1-(4-fluorophenyl)-3-indolyloxy]-1-ethyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[3-(5-Fluorobenzofuran-3-yl)-1-propyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-(5-Fluorobenzofuran-3-yl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-[1-(4-Fluorophenyl)-5-trifluoromethylindazol-3-yl]-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-(5-Trifluoromethylindazol-3-yl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-(4-(1,2-Benzisoxazol-3-yl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],

1-(4-(1,2-Benzisoxazol-3-yl)-1-butyl)spiro[3*H*-2-benzopyran-3,4'-piperidine],

1'-(3-(1,2-Benzisoxazol-3-yl)-1-propyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-(4-(1,2-Benzisothiazol-3-yl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-(3-Indolyl)-1-butyl]-spiro[1,3-benzodioxole-2,4'-piperidine],

1'-(4-(1*H*-Inden-3-yl)-1-butyl)-spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-(Indan-1-yl)-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[4-(1-Indanyl)-but-3-en-1-yl]-spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-(4-(2,3-Dihydro-1-(4-fluorophenyl)-3-indolyl)-1-butyl)spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[3-(Benzo[b]thiophen-3-ylthio)-1-propyl]spiro[isobenzofuran-1(3*H*),4'-piperidine],

1'-[3-(Benzo[b]thiophen-3-ylthio)-1-propyl]spiro[3*H*-2-benzopyran-3,4'-piperidine],

1'-[4-(2,3-Dihydro-benzo[b]thiophen-3-yliden)-1-butyl]spiro[isobenzofuran-1(*3H*),4'-piperidine]-*S,S*-dioxide,

1'-[4-(2,3-Dihydro-benzo[b]thiophen-3-yl)-1-butyl]spiro[isobenzofuran-1(*3H*),4'-piperidine]-*S,S*-dioxide,

1'-[3-(Benzo[b]thiophen-3-yloxy)-1-propyl]spiro[isobenzofuran-1(*3H*),4'-piperidine],

1'-[2-(Benzo[b]thiophen-3-ylmethyloxy)-1-ethyl]spiro[isobenzofuran-1(*3H*),4'-piperidine],

1'-[2-(5-Fluorobenzofuran-3-ylmethyloxy)-1-ethyl]spiro[isobenzofuran-1(*3H*),4'-piperidine],

1'-[2-(Benzofuran-3-ylmethyloxy)-1-ethyl]-4-fluorospiro[isobenzofuran-1(*3H*),4'-piperidine] and

1'-[4-(1-(2-Dimethylamino-1-ethyl)-3-indolyl)-1-butyl]spiro[isobenzofuran-1(3*H*),4'-piperidine].

According to the invention the compounds of formula (I) may be used as the base of the compound or as a pharmaceutically acceptable acid addition salt thereof or as an anhydrate or hydrate of such salt. The salts of the compound used in the invention are salts formed with non-toxic organic or inorganic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethane-disulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Preferably the compound is used as the base or the fumarate.

The acid addition salts according to the invention may be obtained by treatment of 1'-[4-[1-(4-fluorophenyl)-1*H*-indole-3-yl]-1-butyl]-spiro[isobenzo-furan-1(3*H*),4'-piperidine] with the acid in an inert solvent followed by precipitation, isolation and optionally re-crystallisation by known methods and if desired micronisation of the crystalline product by wet or dry milling or another convenient process, or preparation of particles from a solvent-emulsification process.

Precipitation of the salt is preferably carried out in an inert solvent, e.g. an inert polar solvent such as an alcohol (e.g. ethanol, 2-propanol and n-propanol).

WO 9924436 describes the hydrochloride of 1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine] which is a preferred compound according to the present invention.

According to the invention, the compounds of formula (I) or a pharmaceutically acceptable salt thereof may be administered in any suitable way e.g. orally or parenterally, and it may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the compound of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tabletting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

The compound of the invention is most conveniently administered orally in unit dosage forms such as tablets or capsules, containing the active ingredient in an amount from about 10 μg/kg to 10mg/kg body weight, preferably 25 μg/day/kg to 1.0 mg/day/kg, most preferably 0.1 mg/day/kg to 1.0 mg/day/kg body weight.

Pharmacological Tests

The formalin pain model is a well-established animal model of persistent somatic pain (Dubuisson, D. and Dennis, S.G. *Pain 4,* **1977**, 161-174). It has been described as a model

of clinical inflammatory pain (Tjølsen, A. and Hole, K., *In: Dickenson, A.H. and Besson, J.-M.R., Editors,* **1997**. *The Pharmacology of Pain, Springer-Verlag, Berlin,* 1-20). Formalin injected subcutaneously in a hind paw produces initially a local stimulation of the nociceptors, this is referred to as phase 1. This is follow by inflammatory processes and nerve sensitisation (phase 2). The latter phase models the neuropathic pain condition. A number of drugs are active in the model, e.g. morphine and in particular antiepileptic drugs (e.g. gabapentine, lamotrigine, carbamazepine) that have shown beneficial effects in clinical neuropatic states. However, these treatments are accompanied by troublesome side effects. The non-steroid antiinflammatory drugs (NSAIDs) that are used for treatment of inflammatory processes in tissue and have relatively weak effects on neuropathic pain conditions have weak activity in the formalin model.

Experimental Procedure

Fifty microlitres of 2.5% formalin were administered s.c. into the plantar region of the right hind-paw. Following the injection, the animal was placed into an observation chamber, and its subsequent nociceptive behaviour observed. A mirror behind the observation chamber allowed the experimenter an unobstructed view of the injected paw. Observation of the animal's behaviour was made from 0-5 min (phase 1) and 20-30 min (phase 2) following formalin injection. The total time the animal spent licking, biting or shaking the injected paw was recorded. All animals (n=6-10) received a formalin injection and a s.c. injection of either vehicle or test drug 30 min or 2 h before the formalin test.

Results

In Table 1 below percent inhibition of the pain response in phase 2 is given for various doses of 1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine]:

Dosis (mg/kg)	Percent inhibition of pain response
0.5	25
1.5	28

2.5	55
5	62

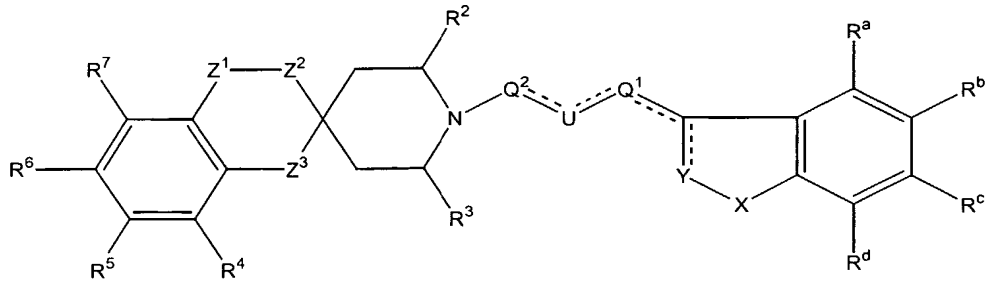
Table 1: *:p< 0.001

The testing of 1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] in the formalin pain model showed that the compound potently inhibited the pain response in phase 2, in a dose dependent manner.

The compound, 1'-[2-(5-Fluorobenzofuran-3-ylmethyloxy)-1-ethyl]spiro[isobenzofuran-1(*3H*),4'-piperidine] also showed potent and dose dependent inhibition of the pain response in phase 2.

Claims

1. The use of a spiro-piperidine compound having the general formula I



(I)

wherein X is CHR^{10}, O, S, SO, SO_2 or NR^{10}, R^{10} being hydrogen, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_3–C_8 cycloalkyl, adamantyl or C_3–C_8 cycloalkyl(C_1–C_6)alkyl, C_3–C_8 cycloalkenyl or C_3–C_8 cycloalkenyl(C_1–C_6)alkyl, C_1–C_6 alkylcarbonyl, phenylcarbonyl, amino(C_1–C_6)alkyl, mono- or di(C_1–C_6)alkylamino(C_1–C_6)alkyl, C_1–C_6 alkylsulfonyl, phenylsulfonyl, or phenyl(C_1–C_6)alkyl or phenyl optionally substituted with one or more substituents independently selected from the following: halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, hydroxy, trifluoromethyl, and cyano, or R^{10} is 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-thiazolyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl;

one or two of the dotted lines may be a bond;
when the dotted line emanating from Y indicates a bond, Y is N or CH; or
when said dotted line indicates no bond, Y is CH_2, NH, C=O or C=S;

R^a – R^d are independently selected from hydrogen, halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, hydroxy, C_1–C_6 alkylthio, C_1–C_6 alkylsulphonyl, C_1–C_6 alkyl- or di(C_1–C_6)alkylamino, cyano, trifluoromethyl, or trifluoromethylthio;

U is CH_2, O or S; or when, one of the dotted lines emanating from U indicates a bond, U is CH; the bond between Q^1 or Q^2, respectively, and U may also be a triple bond and in such case U is "C";

Q^1 is selected from a bond, alkylene or alkenylene and Q^2 is alkylene having at least two C-atoms, alkenylene, or a group Q^3-D wherein Q^3 is alkylene having at least two C-atoms, or alkenylene and D is CR^8R^9 where R^8 and R^9 are independently selected from the substituents defined below for R^4 - R^7, Q^1 and Q^2 having together from 2 to 20 carbon atoms and being optionally substituted with one or more hydroxy groups, any such hydroxy group being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive; and

R^2 and R^3 are independently hydrogen, C_1–C_6 alkyl or they may be linked together thereby forming an ethylene or propylene bridge;

R^4 to R^7 are independently selected from hydrogen, halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, hydroxy, C_1–C_6 alkylthio, C_1–C_6 alkyl- or di(C_1–C_6)alkylamino, cyano, trifluoromethyl, or trifluoromethylthio; and

Z^1 is CH_2, O or S;
Z^2 and Z^3 are independently a bond, CH_2, O or S, with the proviso that Z^1 may not be S or O when Z^2 is S or O, and that Z^2 and Z^3 may not both be a bond;
or Z^1 and Z^2 may together represent a group -CH=CH-;
or when Z^3 is a bond, Z^1 and Z^2 may together represent a 3-membered divalent group containing one O- or S-heteroatom, or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment of neuropathic pain.

2. The use according to Claim **1**, **characterized in,** that the compound of the general Formula **I** used is a compound wherein at least one of Z^1, Z^2 and Z^3 designates O or S.

3. The use according to Claim **2**, **characterized in,** that the compound of the general Formula **I** used is a compound wherein Z^3 is a bond, and Z^2 is O or S and Z^1 is CH_2.

4. The use according to Claim **3**, **characterized in,** that the compound of general Formula I

used is a compound wherein X is O, S or NR^{10} wherein R^{10} is C_1–C_6 alkyl, C_2–C_6 alkenyl, C_3–C_8 cycloalkyl, adamantyl or C_3–C_8 cycloalkyl(C_1–C_6)alkyl, C_3–C_8 cycloalkenyl or C_3–C_8 cycloalkenyl(C_1–C_6)alkyl, C_1–C_6 alkylcarbonyl, phenylcarbonyl, amino(C_1–C_6)alkyl, mono- or di(C_1–C_6)alkylamino(C_1–C_6)alkyl, C_1–C_6 alkylsulfonyl, phenylsulfonyl, or phenyl(C_1–C_6)alkyl or optionally substituted phenyl.

5. The use according to Claim **4**, **characterized in,** that the compound of general Formula I

used is a compound wherein Y is CH and the dotted line emanating from Y indicates a bond.

6. The use according to Claims **3-4**, **characterized in,** that the compound of general Formula I used is a compound wherein X is O.

7. The use according to Claims **3-4**, **characterized in,** that the compound of general Formula I wherein or NR^{10} wherein R^{10} is optionally substituted phenyl.

8. The use according to Claim **1**, **characterized in,** that the compound of the general Formula **I** used is selected from the following:
1'-[2-(5-Fluorobenzofuran-3-ylmethyloxy)-1-ethyl]spiro[isobenzofuran-1(*3H*),4'-piperidine], and
1'-[4-[1-(4-Fluorophenyl)-3-indolyl]-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine], or or a pharmaceutically acceptable salt thereof .

9. The use according to Claim **8**, **characterised in**, that the compound used is 1'-[4-[1-(4 Fluorophenyl)-3-indolyl]-1-butyl]-spiro[isobenzofuran-1(3*H*),4'-piperidine] hydrochloride.

10. A method for the treatment of neuropathic pain **comprising** administering to an individual in need thereof a pharmaceutically acceptable amount of a compound of formula I or a pharmaceutically acceptable salt thereof

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00407

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/537, A61K 31/547
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0004952 A1 (HOECHST AKTIENGESELLSCHAFT), 31 October 1979 (31.10.79) --	1-9
A	US 4524209 A (LARRY DAVIS ET AL), 18 June 1985 (18.06.85) --	1-9
A	US 4521537 A (RAYMOND W. KOSLEY, JR. ET AL), 4 June 1985 (04.06.85) --	1-9
A	WO 9222554 A1 (H. LUNDBECK A/S), 23 December 1992 (23.12.92) -- --------	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2002	07-10-2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00407

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **10**
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/09/02

International application No.
PCT/DK 02/00407

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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/09/02

International application No.
PCT/DK 02/00407

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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/09/02

International application No.
PCT/DK 02/00407

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